

AMENDMENT TO THE SPECIFICATION

On page 1, at line 1, please amend the title and add a cross-reference to related application(s) as follows:

METHOD OF DETERMINING POTENTIAL ALLOSTERICALLY-BINDING
MATRIX METALLOPROTEINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of priority from United States Provisional Patent Application Number 60/268,821, filed February 14, 2001.

AMENDMENTS TO THE CLAIMS

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

Claims 1-45 (canceled).

Claim 46 (new). A method of determining if a compound has potential to allosterically bind to S1' and S1'' sites of MMP-13, the method comprising the steps of:
selecting a compound that comprises first and second hydrophobic groups and first and second hydrogen bond acceptors; and
determining whether the relative positions of centroids of the first and second hydrophobic groups and the first and second hydrogen bond acceptors are present at the following Cartesian coordinates in Å:

- (i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;
- (ii) second hydrogen bond acceptor, 5.08, 2.23, 0.00;
- (iii) first hydrophobic group, -1.52, -3.06, -0.23; and
- (iv) second hydrophobic group, 9.07, 0.00, 0.00;

wherein tolerances in the positions of the hydrophobic groups and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å, respectively.

Claim 47 (new). The method of claim 46, wherein the first hydrophobic group contains a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a 5- or 6-membered monocyclic aromatic group which may contain one or more heteroatoms and which may be 4-substituted or 3,4-disubstituted, but which is of width (including substituents) less than 4.0 Å.

Claim 48 (new). The method of claim 47, wherein the pi-system of the aromatic ring is electron rich.

Claim 49 (new). The method of claim 46, wherein first hydrophobic group, is linked by a first linker chain which is three atoms long to a first 5- or 6-membered ring of the scaffold, the first linker chain atom adjacent to said first scaffold ring forming part of the first hydrogen bond acceptor.

Claim 50 (new). The method of claim 49, wherein the first linker chain has a methylene group located adjacent to the hydrophobic group.

Claim 51 (new). The method of claim 49, wherein the scaffold further comprises a second scaffold ring fused to the first scaffold ring at locations two and three ring atoms distant from the junction between the first scaffold ring and the first linker chain, and the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is two positions distant from said junction forms part of the second hydrogen bond acceptor.

Claim 52 (new). The method of claim 51, wherein the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is three positions distant from said junction has a substituent which is a single atom or is a methyl group.

Claim 53 (new). The method of claim 46, wherein the second hydrophobic group is a 5- or 6-membered aromatic ring which may contain one or several heteroatoms, a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a planar saturated or unsaturated system.

Claim 54 (new). A method of determining if a compound has potential to allosterically bind to S1' and S1'' sites of MMP-13, the method comprising the steps of:
selecting a compound that comprises a first hydrophobic group and first, second and third hydrogen bond acceptors; and
determining whether the relative positions of centroids of the first hydrophobic group and the first, second and third hydrogen bond acceptors are present at the following Cartesian coordinates in Å:

- (i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;
- (ii) second hydrogen bond acceptor, 5.08, 2.23, 0.0;
- (iii) third hydrogen bond acceptor, 7.15, 0.80, 0.00; and
- (iv) first hydrophobic group, -1.52, -3.06, -0.23;

wherein tolerances in the positions of the first hydrophobic group and the hydrogen bond acceptors are $\pm 1.0 \text{ \AA}$ and $\pm 1.5 \text{ \AA}$, respectively.

Claim 55 (new). The method of claim 54, wherein the first hydrophobic group contains a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a 5- or 6-membered monocyclic aromatic group which may contain one or more heteroatoms and which may be 4-substituted or 3,4-disubstituted, but which is of width (including substituents) less than 4.0 \AA .

Claim 56 (new). The method of claim 55, wherein the pi-system of the aromatic ring is electron rich.

Claim 57 (new). The method of claim 55, wherein first hydrophobic group, is linked by a first linker chain which is three atoms long to a first 5- or 6-membered ring of the scaffold, the first linker chain atom adjacent to said first scaffold ring forming part of the first hydrogen bond acceptor.

Claim 58 (new). The method of claim 57, wherein the chain has a methylene group located adjacent to the hydrophobic group.

Claim 59 (new). The method of claim 57, wherein the scaffold further comprises a second ring fused to the first scaffold ring at locations two and three ring atoms distant from the junction between the first scaffold ring and the chain, and the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is two positions distant from said junction forms part of the second hydrogen bond acceptor.

Claim 60 (new). The method of claim 59, wherein the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is three positions distant from said junction has a substituent which is a single atom or is a methyl group.

Claim 61 (new). The method of claim 59, wherein the second scaffold ring is 6-membered and the atom of the second scaffold ring that is two positions distant from the atom that forms part of the second hydrogen bond acceptor forms part of the third hydrogen bond acceptor.

Claim 62 (new). The method of claim 59, wherein the second scaffold ring is 6-membered and a third scaffold ring is fused to the second scaffold ring at those atoms of the second scaffold ring which are two and three positions distant from the atom that forms part of the second hydrogen bond acceptor, an atom of the third scaffold ring forming part of the third hydrogen bond acceptor.

Claim 63 (new). A method of determining if a compound has potential to allosterically bind to S1' and S1'' sites of MMP-13, the method comprising the steps of:
selecting a compound that comprises first and second hydrophobic groups and first, second and third hydrogen bond acceptors; and
determining whether the relative positions of centroids of the first and second hydrophobic groups and the first, second and third hydrogen bond acceptors are present at the following Cartesian coordinates in Å:

- (i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;
- (ii) second hydrogen bond acceptor, 5.08, 2.23, 0.0;
- (iii) third hydrogen bond acceptor, 7.15, 0.80, 0.00;
- (iv) first hydrophobic group, -1.52, -3.06, -0.23; and
- (v) second hydrophobic group, 9.07, 0.00, 0.00;

wherein tolerances in the positions of the hydrophobic groups and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å, respectively.

Claim 64 (new). The method of claim 63, wherein the first hydrophobic group contains a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a 5- or 6-membered monocyclic aromatic group which may contain one or more heteroatoms and which may be 4-substituted or 3,4-disubstituted, but which is of width (including substituents) less than 4.0 Å.

Claim 65 (new). The method of claim 64, wherein the pi-system of the aromatic ring is electron rich.

Claim 66 (new). The method of claim 64, wherein first hydrophobic group, is linked by a first linker chain which is three atoms long to a first 5- or 6-membered ring of the scaffold, the first linker chain atom adjacent to said first scaffold ring forming part of the first hydrogen bond acceptor.

Claim 67 (new). The method of claim 66, wherein the chain has a methylene group located adjacent to the hydrophobic group.

Claim 68 (new). The method of claim 66, wherein the scaffold further comprises a second scaffold ring fused to the first scaffold ring at locations two and three ring atoms distant from the junction between the first scaffold ring and the first linker chain, and the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is two positions distant from said junction forms part of the second hydrogen bond acceptor.

Claim 69 (new). The method of claim 68, wherein the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is three positions distant from said junction has a substituent which is a single atom or is a methyl group.

Claim 70 (new). The method of claim 68, wherein the second scaffold ring is 6-membered and the atom of the second scaffold ring that is two positions distant from

the atom that forms part of the second hydrogen bond acceptor forms part of the third hydrogen bond acceptor.

Claim 71 (new). The method of claim 68, wherein the second scaffold ring is 6-membered and a third scaffold ring is fused to the second scaffold ring at those atoms of the second scaffold ring which are two and three positions distant from the atom that forms part of the second hydrogen bond acceptor, an atom of the third scaffold ring forming part of the third hydrogen bond acceptor.

Claim 72 (new). The method of claim 63, wherein the second hydrophobic group is a 5- or 6-membered aromatic ring which may contain one or several heteroatoms, a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a planar saturated or unsaturated system.

Claim 73 (new). A method of determining if a compound has potential to allosterically bind to S1' and S1'' sites of MMP-13, the method comprising the steps of:

- selecting a compound that comprises a scaffold, first and second hydrogen bond acceptors and first and second hydrophobic groups connected by side chains to the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen bond acceptors; and
- determining whether the first and second hydrogen bond acceptors and the first and second hydrophobic groups are arranged so that:
 - The first and second hydrogen bond acceptors can bind with Thr 245 and Thr 247, respectively, of the MMP-13;
 - The first hydrophobic group can locate within the S1' site; and
 - The second hydrophobic group can be open to solvent.

Claim 74 (new). A method of determining if a compound has potential to allosterically bind to S1' and S1'' sites of MMP-13, the method comprising the steps of:

- selecting a compound that comprises a scaffold, first, second and third hydrogen bond acceptors, and a hydrophobic group connected by a side chain to

the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen bond acceptors; and

determining whether the first, second and third hydrogen bond acceptors, and the hydrophobic group are arranged so that:

The first, second and third hydrogen bond acceptors can bind with Thr 245, Thr 247, and Met 253, respectively, of the MMP-13; and
The hydrophobic group can locate within the S1' site.

Claim 75 (new). A method of determining if a compound has potential to allosterically bind to S1' and S1'' sites of MMP-13, the method comprising the steps of:

selecting a compound that comprises a scaffold, first, second and third hydrogen bond acceptors, and first and second hydrophobic groups connected by side chains to the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen bond acceptors; and

determining whether the first, second and third hydrogen bond acceptors, and the first and second hydrophobic groups are arranged so that:

The first, second and third hydrogen bond acceptors can bind with Thr 245, Thr 247, and Met 253, respectively, of the MMP-13;

The first hydrophobic group can locate within the S1' site; and

The second hydrophobic group can be open to solvent.

Claim 76 (new). The method according to any one of the preceding claims, wherein the compound is a pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione.